

## II. REMARKS

### 1. Formal Matters

#### a.) Action Summary

According to the Office Action, claims 28, 41 and 75-96 stand pending in the application. According to the Office Action, claims 78, 79, 81, 85, 86, 91, 92 and 94-96 stand withdrawn from consideration. All claims stand rejected.

By the amendment presented above, pending claims should now be 28, 41, 75-110.

#### b.) Restriction/Election

It is acknowledged that the restriction/election has been made final (OA at page 2). Applicants reserve the right to petition for reconsideration of the restriction requirement under 37 C.F.R. § 1.144. It is also noted that if independent claims 28 and 41 (which are generic) are held to be allowable, all claims depending therefrom should be allowed as per 37 C.F.R. § 1.141 (also see page 4 of the Restriction Requirement dated June 9, 2006).

#### c.) Objection to the Abstract Under 37 C.F.R. § 1.72

At page 2 of the present Office Action, the Examiner 'objects' to the Abstract. This objection is respectfully traversed.

According to the 'objection': "*The abstract of the disclosure is objected to because it does not allow the public to generally determine quickly from a cursory inspection the **nature and gist** of the invention.*" (OA at page 2, emphasis added in bold). The Action goes on to suggest that the abstract should describe steps a) through e) of either claim 28 or 41.

According to 37 C.F.R. § 1.72(b):

*"A brief abstract of the technical disclosure in the specification must commence on a separate sheet, preferably following the claims, under the heading "Abstract" or "Abstract of the Disclosure." The sheet or sheets presenting the abstract may not include other parts of the application or other material. The abstract in an application filed under 35 U.S.C. 111 may not exceed 150 words in length. **The purpose of the abstract is to enable the United States Patent and Trademark Office and the public generally to determine quickly from a cursory inspection the nature and gist of the technical disclosure.**"*

(37 C.F.R. § 1.72(b), emphasis added)

All that is required of this rule is that the abstract contain enough information to provide the Office and the public with the ***"nature and gist of the technical disclosure"*** based upon a *"cursory inspection"*. The rule does not require that any claim be recited and actually prohibits including: *"other parts of the application or other material"*. Thus, it would seem that the suggestion that claims 28 or 41 be reproduced in the abstract is contrary to the rule.

Definitions for the words, *"nature"*, *"gist"* and *"essence"* from the Merriam-Webster Online Dictionary ([www.m-w.com](http://www.m-w.com)) are attached as Exhibits A, B and C, respectively. According to these exhibits, 1) the word 'nature' is defined as *"the inherent character or basic constitution of a person or thing"*; 2) the word 'gist' is defined as *"the main point or part: ESSENCE"* and 3) the word 'essence' is defined as *"the most significant element, quality, or aspect of a thing or person"*. In the present case, the "thing" referred to in some of the definitions would be the patent application itself.

In the present patent application, the Abstract reads: *"This invention pertains to the field of PNA dimer and PNA oligomer synthesis."* Respectfully, this abstract succinctly states the 'inherent character', the 'main point' and/or the 'most significant element, quality or aspect of the application'. That is, the application pertains to *"PNA dimer and PNA oligomer synthesis"*. Thus, the abstract sufficiently conveys the 'gist, nature and/or essence' of this patent application based upon a 'cursory inspection' as required by the rule. Withdrawal of the 'objection' is therefore respectfully requested.

d) *Information Disclosure Statement(s)*

The Examiner is thanked for return of the various PTO Form 1449s for the various Information Disclosure Statements so far considered.

A supplemental information disclosure statement (IDS) is being filed with this response. This IDS includes new references the significance of which is discussed below. Authorization to deduct that appropriate fee for consideration of said IDS can be found in said IDS. The Examiner is requested to consider the references submitted herewith and return the completed newly submitted PTO-Form 1449 with the next communication from the Office.

**2. Remarks on the Amendment to the Specification:**

An amendment to page 14 of the specification has been requested so that all references to NMP are identical. This amendment is requested to correct a typographical error so that the references to NMP at pages 23 and 28 are consistent with the reference at page 14.

Exhibit D is a printout from the website of sigmaaldrich.com, a well-known vendor of fine chemicals. As can be seen from Exhibit D, 1-Methyl-2-pyrrolidinone is also known as 1-Methyl-2-pyrrolidone and N-Methyl-2-pyrrolidone. This reference is being submitted to demonstrate that the ordinary practitioner identifies the same chemical structure (i.e. the chemical often abbreviated as NMP) with various different chemical names.

**3. Remarks on the Amendment to the Claims:**

The preamble of claims 28 and 41 has been amended to be more concise. A corresponding clarifying amendment has been made in step (e) of claims 28 and 41. Since the preamble is ordinarily given no patentable weight, it is believed that these amendments neither narrow nor expand the claim scope.

Claim 28 has also been amended to delete reference to the limitation: *"but that does not allow for more than 50 percent cyclization and elimination of the first PNA monomer from the support"*. Deletion of this limitation appears to be proper since the present claims were rejected yet no reference teaches this limitation. Thus, it is unnecessary for patentability. Moreover, there is no suggestion in the specification that it is an essential limitation (See Specification at page 22).

Claim 28 has been further amended to address various rejections under 35 U.S.C. 112 as discussed in more detail below. It is believed that while these amendments clarify the claim language, none narrow the claim scope. In fact, as discussed below, it is respectfully submitted that the scope of claim 28 is now broader because the limitations "as soon as is practical" as well as the limitation to cyclization and elimination (discussed above) have been removed.

Claim 77 has been amended for consistency with claim 28.

Claim 81 is amended for consistency with claim 80.

Claim 92 is amended for consistency with claim 91.

New claims 97-110 are added to more distinctly claim the subject matter for which Applicants seek letters patent.

**4. Response to the Rejections under 35 U.S.C. § 112:**

At page 3-4 of the Office Action, claims 28, 75-77, 80 and 82-84 are rejected under 35 U.S.C. § 112, second paragraph as allegedly failing to particularly point out and distinctly claim subject matter for which applicants regard as their invention. It is believed that the amendments to claim 28 address the various issues raised by the Examiner. Further comment is made as follows.

With respect to use of the phrase: "*substantially removes the base labile N-terminal protection group*", the claim has been reworded so that it is clear that the N-terminal protecting group is removed from substantially all of the support bound first PNA monomer. One of skill in the art would appreciate that the protecting group must be removed from the support bound first PNA monomer before a second PNA monomer can be coupled to a first PNA monomer to thereby form a PNA dimer. One of skill in the art would further appreciate that a short treatment of the support with the deprotection reagent may not remove the protecting group from all of the support bound first PNA molecules but that it is sufficient that the protecting group of substantially all of the support bound first PNA monomers be removed. Importantly, the law only requires that the claims be sufficiently clear so that one of ordinary skill in the art (in this case one of skill in the art of PNA synthesis) can understand the claim scope when viewed in light of the specification and the teachings of the art. M.P.E.P. § 2173.02 Support for the amendment can be found throughout the specification as filed; including in the claim as originally drafted. For example, support can be found in the specification at page 22 and in Example 1.

With respect to the assertion that the inclusion of the phrase "*as soon as is practical*" in claim 28 renders it indefinite, that limitation has been removed. While Applicants disagree that the presence of said phrase renders the claim indefinite, particularly in view of the express teachings of the specification at pages 22 and 30, the limitation is not needed to distinguish the subject matter of claim 28 from the prior art. Accordingly, the limitation has been removed and the claim scope is now broader. This limitation is now, however, recited in claim 110.

In view of the amendments and remarks, reconsideration and withdrawal of all rejections under 35 U.S.C. 112, second paragraph is respectfully requested.

**5. Response to the Rejections under 35 U.S.C. § 103(a):**

*(a) The law of 35 U.S.C. § 103(a)*

It is black letter law that the references combined to support a rejection under 35 U.S.C. § 103(a) must teach each and every element/limitation of the claimed subject matter else no *prima facie* case of obviousness exists. Moreover, there must be suggestion or motivation to combine the references coupled with **a reasonable expectation of succeeding** if the elements of the various references are combined in the manner suggested by the rejection. M.P.E.P. 2143

In the absence of a proper *prima facie* case of obviousness, an Applicant is entitled to a patent. *In re Rouffet*, 149 F.3d 1350, 1355, 47 U.S.P.Q.2d 1453, 1455 (Fed. Cir. 1998). To overcome a claimed *prima facie* case of obviousness, an Applicant can either show that the *prima facie* case of obviousness is insufficient **because it relies on incorrect factual predicates** or otherwise present secondary evidence of non-obviousness. *Id.* at 1355, 47 U.S.P.Q.2d 1453 at 1455 (Fed. Cir. 1998).

*(b) Rejection over Breipohl in view of Kovacs, Thomson and Koch*

At page 4 of the Office Action, claims 28, 41, 77, 80, 82-84, 87-90 and 93 are rejected under 35 U.S.C. §103(a) as unpatentable over Breipohl (US Pat. No. 6,121,418) in view of Kovacs (Fourth International Electronic Conference on Synthetic Organic Chemistry (ECSOC-4), [www.mdpi.org/ecsoc-4htm](http://www.mdpi.org/ecsoc-4htm), September 2000), Thomson (Tetrahedron Letters, 51: 6179-6194 (1995) and Koch (J. Peptide Res. 49: 80-88 (1997). This rejection is respectfully traversed.

*(i) The rejection is supported by incorrect factual predicates*

As a preliminary matter, the following incorrect statements made in support of the present rejection are noted in Table 1.

Table 1

Assertion made in support of the rejection	Support in the Action	Actual teaching of the reference	Support in the reference
Kovacs teaches <b>5 minutes</b> in Scheme 2	Page 7	Kovacs teaches 2 x 5 min; which is at least <b>10 minutes</b> of treatment with the deprotection reagent	Page 3 of 8 and again in Scheme 2, page 6 of 8
".. see Koch, page 81, col. 1, lines 1-20 <sup>1</sup> ; and pages 81, col. 2, lines 10-15, wherein <b>3 minutes</b> are taught.."	Page 7	Koch teaches 2 x 3 minutes of treatment with TFA/m-cresol (95/5; 2 x 180 sec (which is at least <b>6 minutes</b> of treatment with the deprotection reagent) to protect the (acid-labile) Boc protecting group. <b>With respect to claim 28, this is non-analogous art.</b>	Page 81, col. 2

Because it is well accepted law that a rejection cannot be premised upon incorrect facts, reconsideration and withdrawal of the rejection of claims 28, 41, 77, 80, 82-84, 87-90 and 93 under 35 U.S.C. §103(a) based upon the combination of *Breipohl in view of Kovacs, Thomson and Koch* is believed to be proper for at least this reason.

- (ii) *The references fail to teach all of the claim elements/limitations*  
*- Claim 28 and claims dependent thereon*

With respect to the rejection of claim 28, not a single reference cited to support the rejection teaches the element of: "... ***treating the solid support for a period of about 1 to about 2 minutes with a deprotection reagent that substantially removes the base labile N-terminal amine protecting group from the support bound first PNA monomer*** ..." (emphasis added). The specific teachings of each reference are summarized in Table 2.

1 The discussion at col. 1 lines 1-20 of Koch discloses a treatment of "several minutes". This is consistent with a teaching of 10 minutes or 15 minutes which is precisely what is taught in Kovacs and Thomson.

Table 2

Reference	Summary of Teaching	Support in Reference
Breipohl	Although Breipohl discusses using reagent solutions comprising DBU or piperidine "for eliminating the base-labile amino protecting group PG", it provides <b>no teaching</b> as to reaction time for this step in either the description or the examples	Col. 7, lines 22-33 and examples 36-40
Kovacs	Kovacs only teaches the preparation of C-terminal amides and not C-terminal acids. <b>In this vain it is non-analogous art.</b> Regardless, the reference specifically teaches the use of 20% piperidine in DMF, 2 x 5 min ( <b>which is at least 10 minutes</b> )	Page 3 of 8 and again in Scheme 2, page 6 of 8
Thomson	Thomson teaches an even longer treatment and stronger treatment with piperidine. Specifically, this reference teaches 3 x 5 min ( <b>which is at least 15 minutes</b> ) with 30% piperidine in DMF	Page 6192 under the heading "Oligomer Synthesis"
Koch	Koch doesn't teach removal of the Fmoc group at all. Rather <b>Koch is non-analogous art</b> because it involves the removal of the acid-labile amine protecting group t-butyloxycarbonyl (t-boc) of the Boc/Z monomers. Although this deprotection step was performed using a treatment of 2 x 180 sec (2 x 3 minutes = 6 minutes), no comparison can be made to the subject matter of claim 28 since claim 28 pertains to the removal of a base-labile amine protecting group and Koch teaches conditions for the removal of an acid-labile protecting group.	Page 81, col. 2.

From Table 2 it is apparent that the references are deficient in an essential teaching. To overcome this obvious deficiency, the Action states:

*"Although Kovacs teaches 5 minutes in Scheme 2 (an incorrect statement as discussed above), one of ordinary skill in the art would have recognized from the teachings of Kovacs that deprotection times of this type require a couple of minutes to complete (a bald assertion for which there is truly no support in the cited references), and are parameters that are routinely adjustable. Such an understanding is evidenced by Koch and Thomson, (see Koch, page 81, col. 1, lines 1-20; and page 81, col. 2, lines 10-15, wherein 3 minutes are taught (another incorrect statement as discussed above); see Thomson on page 6192, last paragraph (Thomson actually teaches 3 x 5 minutes; which is 15 minutes not 3 minutes).<sup>2</sup> Absent any secondary considerations of*

2 It is well accepted that an examiner's bald assertion cannot support a rejection under 35 U.S.C. § 103(a). *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988)

*nonobviousness, the limitation of about 1 to 2 minutes is an obvious variation of the times taught by Kovacs and/or Koch, and is considered routine experimentation. Therefore, the claimed invention as a whole was prima facie obvious at the time it was made"*

(OA at page 7, commentary added in bold)

It is respectfully submitted that this analysis is based in large part on incorrect facts, unsupported assertions and is hindsight based.

It is self-evident that the only cited teachings pertaining to conditions for removal of a base-labile amino protecting group (e.g. Fmoc) with deprotection reagent such as piperidine are Kovacs and Thompson. These references teach treatment with a deprotection reagent for 10 minutes and 15 minutes, respectively. It is also self-evident that comparing the 6 minute deprotection conditions for an acid-labile protection such as is taught by Koch, is analogous to comparing apples to oranges. It is simply improper because it is non-analogous to the subject matter of claim 28.

In his analysis, the Examiner relies heavily in the fact that it had been argued by Koch that base treatment should be minimized because of possible decomposition of the PNA oligomer (OA at page 6). However, this fact was known to Thompson (Koch actually cites reference 11, which is Thomson, as the source for this fact) who taught a deprotection time of 15 minutes as well as by Kovacs (At page 2 of 8, Kovacs cites to references 9 (Thomson) and 10 (cited as **Ref CCL** in the supplemental IDS submitted herewith), both of which describe the acyl transfer and cyclization and elimination reaction of PNA under basic conditions) who taught a 10 minute deprotection regime. That the acyl transfer and cyclization and elimination reactions were long-known in the PNA art are further evidenced by Christensen1 (**Ref CCJ** in the supplemental IDS submitted herewith) and Christensen2 (**Ref CCK** in the supplemental IDS submitted herewith).

So all this all begs the question, if it was long-known that basic conditions cause decomposition of a PNA oligomer and therefore should be minimized, why did the art teach treatment for 10-15 minutes and not 1-2 minutes for the removal of the Fmoc protecting group? Certainly, if these "*are parameters that are routinely adjustable*" as argued by the examiner in support of the rejection (OA at page 7), Thomson and/or Kovacs would have tried something closer to 1-2 minutes – BUT THEY DID NOT!

Taking the data most favorable to support his analysis, the Examiner is basically asserting that 2 minutes (Applicants) is the same 10 minutes (Kovacs). Any chemist would appreciate that a two minute deprotection cycle is a five-fold (or 80%) decrease in



the reaction time taught by the closest reference (i.e. Kovacs). Any chemist would further appreciate all reactions are based on kinetics and that this type of extreme change in reaction time is not routinely attempted without evidence that the reaction can be efficiently carried out.<sup>3</sup> However no reference teaches that the deprotection cycle can be so altered for the removal of the base-labile protecting group of a PNA monomer or PNA oligomer. Thus, the answer to the question posed above is clear. Ordinary practitioners such as Thompson and Kovacs, armed with the knowledge that treatment under basic conditions would cause decomposition, **had no reasonable expectation that an approximate five-fold decrease in the time commonly used for the deprotection of the base-labile amine protecting group (e.g. Fmoc) of a PNA monomer or PNA oligomer would be successful.**

In short, the Examiner's analysis is hindsight based. The Examiner uses knowledge supplied only by the specification (i.e. that the deprotection of the Fmoc group on a PNA monomer or PNA oligomer can be efficiently performed in 1-2 minutes) and asserts that to achieve this result is mere routine adjustment obvious to anyone in the art motivated to minimize the reaction time so as to avoid unwanted decomposition. However, Thomson and Kovacs, who were aware of the problem and thus sufficiently motivated in the manner suggested by the Examiner in support of the rejection, didn't chose the alleged 'obvious' solution. From this alone it is clear that the alleged 'obvious' solution is not so obvious. In fact, that Thomson and Kovacs didn't modify the deprotection conditions in the manner asserted as being obvious, suggests that this approach may not have even been 'obvious to try' (which of course is a lower standard and not the standard of obviousness under 35 U.S.C. § 103(a)).

In view of the foregoing, reconsideration and withdrawal of the rejection of claim 28 and claims dependent thereon under 35 U.S.C. §103(a) based upon the combination of *Breipohl in view of Kovacs, Thomson and Koch* is believed to be proper for at least this reason.

- *Claim 41 and claims dependent thereon*

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<sup>3</sup> Curiously Koch actually performed the necessary kinetic analysis with respect to the initial removal of the acid-labile t-boc protecting group from the linker of the support. (Koch at page 82-83, bridging paragraph)

With respect to the rejection of claim 41, not a single reference cited to support the rejection teaches the element of: "... wherein the final loading of the PNA dimer on the support is greater than or equal to 0.08 mmol per gram". Although the present Office Action alleges that Rink resin<sup>4</sup> provides a loading of greater than 0.08 mmol per gram (OA at page 5), as can be seen from Example 1 in Applicants' specification the initial loading is an irrelevant number since the chemistry is not 100 percent efficient and weight is being added to the support during each synthetic cycle. In particular, it is apparent from Example 1 that the loading drops significantly with each successive reaction cycle. Accordingly, the initial loading is not reasonably related to the loading of dimer on the support after two synthetic cycles have been performed.

In view of the foregoing, reconsideration and withdrawal of the rejection of claim 41 and claims dependent thereon under 35 U.S.C. §103(a) based upon the combination of *Breipohl in view of Kovacs, Thomson and Koch* is believed to be proper for at least this reason.

- Summary

In summary, it is respectfully submitted that no *prima facie* case for obviousness of any of the subject matter of claim 28, 41 or 75-96 has been demonstrated. Reconsideration and withdrawal of the rejection of claims 28, 41, 77, 80, 82-84, 87-90 and 93 under 35 U.S.C. § 103(a) over *Breipohl in view of Kovacs, Thomson and Koch* is respectfully requested.

(c) *Rejection over Seitz in view of Thomson and Koch*

At page 7, claims 28, 75 and 77 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Seitz, in view of Thomson and Koch. This rejection is respectfully traversed.

This rejection follows the logic asserted with respect to the rejection of claims 28, 41, 77, 80, 82-84, 87-90 and 93 under 35 U.S.C. §103(a) over *Breipohl* (US Pat. No. 6,121,418) in view of Kovacs (Fourth International Electronic Conference on Synthetic Organic Chemistry (ECSOC-4), [www.mdpi.org/ecsoc-4.htm](http://www.mdpi.org/ecsoc-4.htm), September 2000), Thomson

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<sup>4</sup> In footnote 1 of the Office Action there is a significant discussion of incorporation by reference of the prior art disclosure: H. Rink, *Tetrahedron Letters* 1987, 3787-3790).

(Tetrahedron Letters, 51: 6179-6194 (1995) and Koch (J. Peptide Res. 49: 80-88 (1997)). As noted above, no reference teaches the element of: "... *treating the solid support **for a period of about 1 to about 2 minutes** with a deprotection reagent that substantially removes **the base labile N-terminal amine protecting group** from the support bound first PNA monomer ...*" (emphasis added). Regardless, the present Office Action attempts to explain this deficiency away as being an obvious variation of conditions described in the references cited. However, for the reasons discussed above, this argument is flawed. In particular, the presently claimed subject matter is not a merely routine adjustment of experimental parameters for removal of a base-labile amine protecting group from a PNA monomer or PNA oligomer. Thus, there is no reasonable expectation of succeeding in achieving the presently claimed subject matter based upon the teachings of the references as combined in support of the rejection.

In view of the foregoing, it is respectfully submitted that no *prima facie* case for obviousness of any of the subject matter of claims 28, 75 or 77 has been demonstrated. Reconsideration and withdrawal of the rejection of claims 28, 75 and 77 under 35 U.S.C. § 103(a) over Seitz, in view of Thomson and Koch is respectfully requested.

## 6. Patentability of the newly cited claims

New independent claim 97 differs from claim 28 in that it requires that the first PNA monomer be linked directly to the linker of the solid support. Antecedent basis for this embodiment can be found, for example, in Example 1 of the application as filed.

The primary reference, Breipohl, in the first rejection set forth above teaches PNA oligomers of Formula I (at col. 1) wherein A and Q are amino acids (not PNA monomers). In particular, the residue Q is the C-terminal residue that is linked to the linker of the support (see Structure Ia at col. 2). Thus, it cannot be said that Breipohl teaches one to link the first PNA monomer directly to the linker of the solid support. Thus, there is independent basis for arguing the patentability of claim 97 and claims dependent thereon.

## III. SUMMARY

It is believed that this response addresses all issues set forth in the present Restriction Requirement and the application is in ready condition for allowance. In

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For the convenience of the Office, this reference is now presented as **Ref CCI** in the

consideration of the preceding amendments and remarks, Applicants hereby respectfully request reconsideration of all pending claims, the withdrawal of all rejections set forth in the present Action and issue of a Notice of Allowance by The Office.

#### IV. INTERVIEW

If the Examiner believes a telephonic or personal interview would advance the prosecution of the subject application, the Examiner is invited to contact attorney Gildea during business hours at the telephone or facsimile numbers listed below.

#### V. FEES

A petition under 37 C.F.R. § 1.136(a) for a two month extension, and authorization to deduct the appropriate fee from Deposit Account No. 01-2213 accompanies said petition.

A supplemental Information Disclosure Statement (IDS) is being filed with this submission. Authorization to make an appropriate charge to Deposit Account No. 01-2213 accompanies said IDS.

According to the fee calculation sheet in PAIR dated August 4, 2006, fees for 24 total claims, 6 independent claims and a surcharge for multiple dependent claims have thus far been paid to the Office with respect to the present application. Upon entry of this amendment, this application will contain 39 total claims and 3 independent claims. The following calculations indicate that a fee of \$750.00 is due the Office for entry of this amendment and for the consideration of the amended set of claims.

Total Claims	–	Claims Paid	=	Claims to be Paid	x \$50.00	Totals
39	–	24	=	15	\$ 650.00	\$ 750.00
Total Ind. Claims		Ind. Claims Paid		Ind. Claims to be Paid	x \$ 200.00	
3		6		0	\$ 0	\$ 0
Total Due Office						\$ 750.00

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supplemental IDS submitted herewith.

The Office is hereby authorized to deduct the fee due, believed to be \$750.00, for entry of this amendment set forth herein from Deposit Account 01-2213 (Invoice No. BP0206US-CN1). **A duplicate of this page is included with this submission.** No other fees are believed to be due to The Office for consideration of this paper. If however, The Office determines that any fee is properly due for its consideration of this paper, authorization is hereby granted to charge any required fee associated with the filing or proper consideration of this paper to Deposit Account 01-2213 (Invoice No. BP0206US-CN1).

VI. CORRESPONDENCE/CUSTOMER NUMBER

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Respectfully submitted  
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April 18, 2007  
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